WITHDRAWAL OF REJECTIONS

The rejection states that the rejection of claims 1, 7-10, 21, 27, 44, 63-74 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of pulmonary hypertension with the PDE5 inhibitor of sildenafil, does not reasonably provide enablement for the prevention of pulmonary hypertension with the PDE5 inhibitor sildenafil, is withdrawn in response to the amendment of December 29, 2003.

The rejection states that the rejection of claims 1, 7, and 9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment of December 29, 2003.

The rejection states that the rejection of claims 1 and 7 under 35 U.S.C. 102(b) as being clearly anticipated by Takahashi, et al., which has a publication date of 19961997 for the instantly claimed compound entitled d) of claim 1 is withdrawn in response to the amendment of December 29, 2003.

The rejection states that the rejection of claims 1, 7, and 9 under 35 U.S.C. 103(a) as being unpatentable over Kato et al. of JP 09059159 A2, which has an issue date of March 4, 1997 for the instantly claimed compound entitled d) of claim 1 is removed in response to the amendment of December 29, 2003.

Applicants acknowledge the withdrawal of the above rejections.

35 U.S.C. 103

Claims 1, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al., which has a publication date of 1996/1997 for the instantly claimed compound entitled d) of claim 1. The rejection states that Takahashi et al. describe the administration of E4021, which is a type V phosphodiesterase inhibitor. The rejection also states that Takahashi et al. are directed to the administration of a type V phosphodiesterase inhibitor to protect against the development of right ventricular overload and medial thickening of pulmonary arteries in order to treat pulmonary hypertension. The rejection notes that the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill

in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug.

The rejection also states in direct response to Applicants' previous submission that Applicants argue that there is no motivation or suggestion that the claimed PDE V inhibitors could or should be tried in the treatment of pulmonary hypertension. The rejection states that in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. The rejection also states that so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The rejection further states that Takashi et al., however, do teach that the relaxation of vascular smooth muscle cell is shown to be related to increases in intracellular cGMP. The rejection also states that moreover, Takashi et al teach and provide motivation to use type V phosphodiesterase inhibitors because it is known in the art the that type V phosphodiesterase inhibitors are known to relax a variety of vascular smooth muscle cells in vitro and in vivo. The rejection concludes that accordingly, the skilled artisan is clearly provided with the motivation to use any type V phosphodiesterase inhibitor for the vascular smooth muscle relaxation (vasodilation) in mammals with pulmonary hypertension.

Applicants traverse the rejection of claims 1, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. Applicants submit that the claims are not obvious in light of Takahashi et al. Applicants submit that the art must be taken as a whole and that a review of the full publication of Takahashi et al. (previously submitted) does not provide a sufficient basis for a prima facie case.

Applicants further submit that even assuming arguendo that the reference relied on by the Examiner makes Applicants' invention "obvious to try", "obvious to try" is not the proper standard for patentability. Further, the Examiner has not made out a *prima facie* case of obviousness because, *inter alia* (1) the references provide no effective motivation or suggestion that the claimed PDE V inhibitors could or should be tried in the treatment of pulmonary hypertension and (2) even allowing, *arguendo*, that any such suggestion or motivation were found in these references, the references provide no reasonable expectation of success.

The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Applicants submit that the last sentence of the reference clearly summarizes the content of the reference "Our results suggest that the type V phosphodiesterase inhibitor, E4021, administered orally may prove efficacious in the management of patients with pulmonary hypertension and right ventricular overload" (underlining added for emphasis). Applicants submit that even assuming arguendo that there is a suggestion in the art to use Applicants' claimed compounds to treat pulmonary hypertension there is clearly not a reasonable expectation of success since the author admits that further work must be done and that there is only a suggestion that the type V PDE inhibitors may work. This is a classic instance of an invitation to conduct further experimentation. Further, the rejection itself does not address the issue of reasonable expectation of success (it is completely silent as to this necessary element) which is a requirement under the law. Accordingly, the obviousness rejection is clearly not commensurate with the CAFC standards of patentability as described above.

Further, Takahashi et al. in the penultimate paragraph states

> "A limitation of our study was the E4021 was administered before, not after, the development of right ventricular hypertrophy and medial thickening of pulmonary arteries. That is, the therapeutic administration of the drug was started 24 hours after the injection of monocrotaline. To gain a further indication of the potential clinical efficacy of E4021, a study should be conducted to assess the effects of E4021 administration beginning 4 weeks after monocrotaline injection, the time at which right ventricular hypertrophy and medial thickening are established. Moreover, it was unclear whether 100 mg/kg/day was an optimal dose for E4021 in terms of protection of the development of righ

> ventricular hypertrophy and medial thickening of pulmonary arteries. We should examine whether lower doses of E4021 may be similarly effective. Further, adverse effects of E4021 at these doses need to be determined." (underlining added for emphasis)

Thus, Takahashi et al. further acknowledges the limitations of the study.

Claims 1 and 7-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902 possessing a publication date of December 22, 1994, especially for sildenafil and its derivatives. The rejection states that Ellis et al. teach compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). The rejection also states that this selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The rejection also states that the skilled artisan would have been motivated to treat patients with pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension. The rejection also states that Ellis et al. specifically teach inhibitors of cGMP PDEs with the compounds of formula (I). The rejection notes that Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12}))-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). The rejection also states that Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). The rejection states that Ellis et al. teach various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). The rejection states that Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The rejection reasons that the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug.

The rejection also states, in direct response to Applicants' previous submission, that Applicants argument is unpersuasive because Ellis et al. specifically teach and

provide motivation to the artisan to use PDE V inhibitors to treat pulmonary hypertension, (see page 2, 2nd full paragraph). The rejection states that clearly this provides the skilled artisan with motivation to use an inhibitor of PDE V to treat pulmonary hypertension. The rejection states that "in addition, the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning." The rejection also states that so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin,* 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The rejection also states that Applicants intimate that Ellis et al. do not relate the treatment of pulmonary hypertension to PDE V inhibition. The rejection states that however, Ellis et al. teach that inhibitors of cGMP-PDE clearly teach of treating hypertension and pulmonary hypertension, (see page 2). The rejection points out that in fact, Ellis et al. refer to EP 463,756, which in turn teaches of pyrazaolopyrimidinone compounds, which clearly render the instant invention obvious. The rejection states that the skilled artisan would have been motivated to use sildenafil and other PDE inhibitors to treat pulmonary hypertension. The rejection states that due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension, it would have been inherent that this particular compound of sildenafil is also a PDE V inhibitor. The rejection also states that the fact that applicants have further specified a particular isozyme of this enzyme, in this case the type V isozyme of PDE is an inherent trait or property with the administration of the compounds of Ellis et al. as well as EP 463,765. The rejection concludes that accordingly, it would have been obvious to the skilled artisan to use the very same PDE inhibitory compounds, such as sildenafil, to treat pulmonary hypertension.

Applicants traverse the rejection of claims 1 and 7-112 under 35 U.S.C. 103(a) as being unpatentable over Ellis et al.

Applicants claims are directed to the use of a cGMP PDE **V** inhibitor (i.e., sildenafil) for the treatment of e.g., pulmonary hypertension (underlining and bold added for emphasis).

Initially, Applicants strongly object to the characterization in the rejection's response to Applicants' previous comments that:

"Due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension, it would have been inherent that this particular compound of sildenafil is also a PDE V inhibitor."

This is a mischaracterization of the prior art. Neither EP 0463756, EP-A-0526004, nor Ellis et al. disclose the use of sildenafil for the treatment of pulmonary hypertension. EP 0463756 describes that cGMP PDE inhibitors are useful for treating various disorders; EP 0463756 does not mention the use of any cGMP PDE inhibitors for the treatment of pulmonary hypertension. While EP0526004 does describe that certain cGMP PDE inhibitors are useful for treating pulmonary hypertension EP0526004 does not describe the use of Applicant's claimed compound sildenafil for any indication. Finally, since Ellis et al. refers to both EP 0463756 and EP-A-0526004 in its disclosure regarding pulmonary hypertension Ellis et al. is only disclosing as much as those references disclose -"This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004" (Ellis et al. page 2, second full paragraph). Accordingly, neither EP 0463756, EP-A-0526004, nor Ellis et al. disclose the use of sildenafil for the treatment of pulmonary hypertension. Further, the rejection's comments regarding inherency "it would have been inherent that this particular compound [of] sildenafil is also a PDE V inhibitor" are not applicable since none of the three references disclose the use of sildenafil for the treatment of pulmonary hypertension. In addition, while the rejection also states the "type V isozyme of PDE is an inherent trait or property with the administration of the compounds of Ellis et al. as well as EP 463,765" Applicants again note that neither Ellis et al. nor EP 463,765 disclose the use of sildenafil for the treatment of pulmonary hypertension.

Applicants submit that even assuming arguendo that Ellis et al.makes Applicants' invention "obvious to try", "obvious to try" is not the proper standard for patentability. Further, the Examiner has not made out a *prima facie* case of obviousness because, *inter alia* (1) the reference provides no effective motivation or suggestion that sildenafil could or should be tried in the treatment of pulmonary hypertension and (2) even allowing, *arguendo*, that any such suggestion or motivation were found in this reference, the reference provides no reasonable expectation of success.

The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Applicants submit that their claims are unobvious in light of Ellis et al. at least because the proper framework for determining *prima facie* obviousness in this case is to consider all of the relevant art, both that relied on by the Examiner and that cited by Applicants in the Information Disclosure Statements ("IDSs") of record and submitted herewith. Thus, the art as a whole must be considered. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988). Further, it is well-settled that "all of the relevant teachings of the cited references must be considered in determining what they fairly teach to one having ordinary skill in the art." *In re Mercier*, 515 F.2d 1161, 1165 (C.C.P.A. 1975); *In re Meinhart*, 392 F.2d 273, 276 (C.C.P.A. 1968). Essentially, one cannot pick and choose which references to rely on and thus emphasize some and ignore others to reach a conclusion of obviousness.

As applied to Applicants' claims other research papers show the state of research in the field of pulmonary hypertension at or about the time of Applicants' filing date. Applicants submit that the art was one of hypothesis drawing, calls for further research and statements regarding the possibilities of treatment that the research had provided. Specifically, the obviousness rejection must consider such references as Hansanato, et al., American Journal of Physiology, August 1999, vol. 277(2), L225-L232 which was published just prior to the filing of Applicants' application and is evidence of the state of the art at the time.

> "We measured cyclic nucleotide levels in this study and found that long-term treatment with E-4010 (a selective PDE5 inhibitor) increased cGMP levels in lung but not in aortic tissue and did not change camp levels in these tissues. These results suggest that E-4010 is more effective in lung

than in aortic tissue and is specific to cGMP, supporting our hypothesis that chronic treatment with a selective PDE5 inhibitor would preferentially decrease cGMP degradation rate and increase [cGMP], in lung tissue due to the predominant distribution of this isoenzyme in the lung. This may be the reason why selective PDE5 inhibitors have pulmonary selectivity. Although we investigated in the present study the chronic effects of E-4010 on the development of hypoxia-induced PH only, one previous study (31[Takahashi et al. described above]) has demonstrated the protective effects of another selective PDE5 inhibitor, E-4021, on the development of right ventricular overload and medial thickening of pulmonary arteries in a different rat model of PH, i.e., monocrotaline-induced PH. In addition, several laboratory and clinical studies (15, 17, 22) have shown that PDE5 inhibitors potentiate the vasodilator effects of inhaled NO. Taken together, these reports suggest the possibility that selective PDE5 inhibitors may be useful in the treatment of PH.

In summary, data of this study have shown that an orally active selective PDE5 inhibitor, E-4010, caused selective pulmonary vasodilation and attenuated the increase in PAP, right ventricular hypertrophy, and pulmonary arterial remodeling induced by chronic hypoxia. These hemodynamic effects of E-4010 were associated with an increase in cGMP levels in lung but not in aortic tissue. These results suggest that E-4010 prevented the development of chronic hypoxia-induced PH, probably through increasing cGMP levels in the pulmonary vascular smooth muscle. We conclude that selective PDE5 inhibitors, including e-4010, may provide a new strategy for the treatment of PH." (underlining added for emphasis)

As described above, throughout the Hansanato et al. document's concluding paragraphs are the caveats that obviate any reasonable likelihood of success. Such qualifiers as "suggest, hypothesis, possibility, may" are continuously used to describe the results of the experiments and predictive value thereof. This is simply not consistent with the standards of obviousness as described in the preceding caselaw descriptions and the requirement for a reasonable likelihood of success.

Even the Takahashi et al. reference cited in the rejection is relevant to an understanding of the art as a whole. In that reference, which is more recent than the Ellis et al. reference, research was conducted on whether a PDE5 inhibitor would have functional activity that could possibly predict a viable treatment for pulmonary hypertension. As described above, in light of the Takahashi et al. more recent research there was only a suggestion that the type V PDE inhibitors may be effective for the treatment of pulmonary hypertension. This was described above as a classic instance of an invitation to conduct further experimentation without the necessary

element of a reasonable expectation of success. This reference along with others cannot be ignored in the obviousness analysis, while focusing solely on Ellis et al. Clearly, Takahashi et al., a more recent research paper, reinforces the tenet that there is not a reasonable expectation of success of a PDE5 inhibitor i.e., sildenafil being an effective treatment for pulmonary hypertension. Further research must be performed.

Further neither EP 0463756 nor EP0526004 describe the use of Applicants' claimed compound, sildenafil, to treat pulmonary hypertension. Again, Applicants submit that the art must be taken as a whole and both EP 0463756 and EP0526004 are the basis for the Ellis et al. passage referred to in the rejection. While EP 0463756 describes that cGMP PDE inhibitors are useful for treating various disorders, EP 0463756 does not mention the use of any cGMP PDE inhibitors for the treatment of pulmonary hypertension. Applicants submit that the absence in EP 0463756 of the recitation of pulmonary hypertension (in a lengthy list of other indications) as an indication for cGMP PDE inhibitors strongly implies that cGMP PDE inhibitors are not useful for the treatment of pulmonary hypertension (at a minimum it certainly does not provide a reasonable likelihood of success).

In addition, since sildenafil is included in EP 0463756 and since EP 0463756 implies that sildenafil is not useful for the treatment of pulmonary hypertension, Applicants' claims directed to the use of sildenafil are not obvious in light of the art when taken as a whole.

Further, while EP0526004 does describe that certain cGMP PDE inhibitors are useful for treating pulmonary hypertension, EP0526004 does not describe the use of Applicant's claimed compound, sildenafil, for any indication.

Accordingly, Applicants submit that when the art is taken as a whole (which it must be) a careful review of Ellis et al.'s statement regarding the utility of the cGMP PDE compounds, along with a review of the references (i.e., EP-A-0463756 and EP-A-0526004) that form a basis for Ellis's statement do not suggest or provide a reasonable likelihood of success that sildenafil would be useful in the treatment of pulmonary hypertension. In the pertinent passage Ellis et al. states "utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004 namely in the treatment of ...". Thus, Ellis et al. is referring to the utilities disclosed in EP-A-0463756 for the compounds of EP-A-0463756 and Ellis et al. is referring to the utilities disclosed in EP-A-0526004 for the compounds disclosed in EP-A-0526004. However, as is stated in the paragraph immediately above, EP 0463756 does not mention the use of any cGMP PDE

inhibitors for the treatment of pulmonary hypertension and EP0526004 does not describe the use of any of Applicants' claimed compound, sildenafil, for any indication. While EP-A-0526004 does mention the use of certain cGMP PDE inhibitors for the treatment of pulmonary hypertension it does not suggest that Applicants' claimed compound, sildenafil, would be useful for the treatment of pulmonary hypertension or that there is a reasonable likelihood of success for such treatment. Again, EP 0463756 is silent as to pulmonary hypertension.

Applicants submit that Ellis et al. does not provide a reasonable expectation of success that Applicants' claimed compound, sildenafil, would be useful for the treatment of pulmonary hypertension since, for example, Ellis et al., does not relate the treatment of pulmonary hypertension to PDE V inhibition. Ellis et al. (merely through the EP0526004 reference) relates the treatment of pulmonary hypertension to generalized cGMP PDE inhibition.

Applicants claims are for example, directed to the use of a cGMP PDE V inhibitor (i.e.,, sildenafil) for the treatment of e.g., pulmonary hypertension. Applicants submit that the art must be taken as a whole and both EP 0463756 and EP0526004 are relevant since they are described in the Ellis et al. passage that is referred to in the rejection and they are the basis for that Ellis et al. passage. In the pertinent passage in Ellis et al., EP 0463756 and EP0526004 there is description of the utility of cGMP PDE inhibitors but no mention of a cGMP PDE **V** inhibitor utility (or that any cGMP PDE **V** activity of the recited compounds would be useful for the treatment of pulmonary hypertension). Thus, there is no suggestion that cGMP PDE V inhibitors would be useful for the treatment of pulmonary hypertension or that there is a reasonable likelihood of success for that utility (both being a requirement under current law). There are a number of isoforms of cGMP PDE and cGMP PDE V is only one possibility.

Claims 1, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902, which has a publication date of December 22, 1994, for the instantly claimed compounds entitled c) and e) and f) of claim 1. The rejection states that Ellis et al. teach compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). The rejection states that the selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The rejection states that Ellis et al. specifically teach inhibitors of cGMP PDEs with the compounds of formula (I). The

rejection notes that Ellis et al. disclose of "{a} particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-proply; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). The rejection states that the compounds disclosed by Ellis et al. have a structurally similar core structure with the 1,3-diaziny-4-keto moiety and other identical substituents on position no. 2 of the 1,3-diaznyl ring moiety. The rejection also states that the physiological activities are analogous. The rejection states that the claims differ from the prior art by having an imidazole moiety and an indole moiety, respectively instead of the pyrazole moiety of Ellis et al. The rejection also states that Ellis et al. teach pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Ellis et al. teach of various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). The rejection states that Ellis et al. further teach a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The rejection also states that the determination of a dosage having the optimium therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maxijum effect of the drug. The rejection reasons that one having ordinary skill in the art would have been motivated to select the claimed compound with the expectation that a substitution of a heterocyclic ring moiety, such as imidazole or indole moieties, for another, namely a pyrazole moiety, would not significantly alter the analogous properties of the compound of the reference due to the close structural similarity of the compounds. The rejection concludes that for these reasons the instantly claimed compounds entitled c) and e) and f) of claim 1 are rendered obvious over Ellis et al.

Applicants traverse the rejection of claims 1, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Ellis et al.

Applicants submit that claims 1, 7 and 9 are not obvious over Ellis et al. at least for the reasons described in the response above. However, in an effort to expedite prosecution Applicants have amended the claims (by deleting claims 1 and 7 and amendment of claim 9 to be dependent from 21) such that they are not directed to the compounds "entitled c) and e) and f) without waiver or prejudice against refilling. Applicants submit that such amendment obviates this rejection.

OBVIOUSNESS TYPE DOUBLE PATENTING

The rejection states that the nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ 2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

The rejection states that a timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

The rejection states that effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer and that a terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection states that claims 1, 7-10 and 21-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 8 of U.S. Patent No. 5,250,534. The rejection states that although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant invention and the prior art teach of the treating of hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I).

The rejection states that claims 1, 7-10 and 21-112 are directed to an invention not patentably distinct from claims 1-4 of commonly assigned of U.S. Patent No. 5,250,534. The rejection states that specifically, U.S. Patent No. 5,250,534 teaches of the treatment of hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I).

Applicants submit that they have assumed that the obviousness-type double patenting rejection and the "not patentably distinct" are the same. Applicants specifically note that the "not patentably distinct" rejection did not raise an issue of 101 double patenting. If Applicants' assumption is incorrect, clarification is requested. Applicants

herein reply to an obviousness-type double patenting rejection (see MPEP page 800-22).

Applicants submit that a claim directed to the treatment of pulmonary hypertension with sildenafil is distinct and unobvious over a claim to the treatment of hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I). Applicants submit that the treatment of pulmonary hypertension is unobvious from the treatment of hypertension. There is a vast array of pharmaceutical agents for the treatment of hypertension e.g., alpha blockers, calcium channel blockers, ace inhibitors etc. Goodman & Gilman's "The Pharmacological Basis of Therapeutics" ninth edition J. G. Hardman et al. has a whole chapter (33) directed to the treatment of hypertension entitled "Antihypertensive Agents and the Drug Therapy of Hypertension" that lists and discusses a plethora of antihypertensive agents. Yet, pharmaceutical agents effective for the treatment of pulmonary hypertension are exceedingly few. In addition, well-known antihypertensive agents such as NORVASC, CARDURA etc. are ineffective for the treatment of pulmonary hypertension. Accordingly, one would not have a **reasonable likelihood of success (as described above this is a requirement for obviousness)**, viewed in light of the prior, that a antihypertensive agent would be effective for the treatment of pulmonary hypertension. In fact, given the paucity of treatments for pulmonary hypertension, and the fact that so many antihypertensive agents are ineffective for the treatment of pulmonary hypertension, one would believe that it was unlikely that any particular hypertensive agent (merely on the basis of being an antihypertensive agent) would be useful for the treatment of pulmonary hypertension. Thus, the use of sildenafil for the treatment of pulmonary hypertension is not obvious in light of the use of PDE agents to treat hypertension because the treatment of hypertension does not provide a reasonable expectation that a such treatment would be effective for the treatment of pulmonary hypertension.

The rejection states that claims 1, 7-10 and 21-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 4 of U.S. Patent No. 5,346,901. The rejection states that although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant invention and the prior art teach of the treating hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I).

The rejection states that claims 1, 7-10 and 21-112 are directed to an invention not patentably distinct from claims 1, 2 and 4 of commonly assigned of U.S. Patent No. 5,346,901. The rejection states that specifically, U.S. Patent No. 5,346,901 teaches of the treating of hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I).

Applicants submit that they have assumed that the obviousness-type double patenting rejection and the "not patentably distinct" are the same. Applicants specifically note that the "not patentably distinct" rejection did not raise an issue of 101 double patenting. If Applicants' assumption is incorrect, clarification is requested. Applicants herein reply to an obviousness-type double patenting rejection (see MPEP page 800-22).

Applicants submit that a claim directed to the treatment of pulmonary hypertension with sildenafil is distinct and unobvious over a claim to the treatment of hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I). Applicants submit that the treatment of pulmonary hypertension is unobvious from the treatment of hypertension. There is a vast array of pharmaceutical agents for the treatment of hypertension e.g., alpha blockers, calcium channel blockers, ace inhibitors etc. Goodman & Gilman's "The Pharmacological Basis of Therapeutics" ninth edition J. G. Hardman et al. has a whole chapter (33) directed to the treatment of hypertension entitled "Antihypertensive Agents and the Drug Therapy of Hypertension" that lists and discusses a plethora of antihypertensive agents. Yet, pharmaceutical agents effective for the treatment of pulmonary hypertension are exceedingly few. In addition, well-known antihypertensive agents such as NORVASC, CARDURA etc. are ineffective for the treatment of pulmonary hypertension. Accordingly, one would not have a **reasonable likelihood of success (as described above this is a requirement for obviousness)**, viewed in light of the prior art, that a antihypertensive agent would be effective for the treatment of pulmonary hypertension. In fact, given the paucity of treatments for pulmonary hypertension, and the fact that so many antihypertensive agents are ineffective for the treatment of pulmonary hypertension, one would believe that it was unlikely that any particular antihypertensive agent (merely on the basis of being an antihypertensive agent) would be useful for the treatment of pulmonary hypertension. Thus, the use of sildenafil for the treatment of pulmonary hypertension is not obvious in light of the use of PDE agents to treat hypertension because the treatment of hypertension does not provide a reasonable

expectation that such treatment would be effective for the treatment of pulmonary hypertension.

The rejection states that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP §2302) and that commonly assigned of U.S. Patent No. 5,250,534 and 5,346,901, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. The rejection states that in order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. The rejection states that failure to comply with this requirement will result in a holding of abandonment of the application.

The rejection states that a showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Applicants traverse the "provisional" rejection that commonly assigned U.S. Patent No. 5,250,534 and 5,346,901, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made.

In accordance with M.P.E.P. 706.02(1)(2); page 700-39 Applicants herein provide the following statement.

"U.S. Application serial no. 09/692,807 and patents 5,250,534 and 5,346,901 were, at the time the invention of U.S. Application serial no. 09/692,807 was made, owned by Pfizer Inc."

Accordingly, Applicants submit that the "provisional" rejection has been obviated.

Based on the foregoing, favorable action on claims 8-10 and 21-112 is requested.

Applicants include herein a Supplemental Information Disclosure Statement.

Authorization is hereby provided to charge the fee for the Supplemental

Information Disclosure Statement any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully Submitted,

11/1/04
Date

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